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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/940,941	08/28/2001	Atsushi Sogabe	211352	6205

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EXAMINER

SLOBODYANSKY, ELIZABETH

ART UNIT PAPER NUMBER

1652

DATE MAILED: 02/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/940,941

Applicant(s)

SOGABE ET AL.

Examiner

Elizabeth Slobodyansky

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 28 August 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 24-42 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 24-42 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 28/8/01 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☒ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. 08/799,897.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2,4.

- 4) ☒ Interview Summary (PTO-413) Paper No(s) 3.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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### **DETAILED ACTION**

This application is a reissue of application 08/799,897 issued as US Patent 6,080,553.

Claims 1-23, from the issued patent, have been canceled. Claims 24-42 have been added.

Claims 24-42 are under consideration.

### ***Information Disclosure Statement***

The reference cited on the information disclosure statement filed January 31, 2002 was lined through because it was previously cited on form PTO-1449 filed August 28, 2001. The attached translation has been placed in the application file and considered.

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### ***Drawings***

The drawings filed concurrently with the application have been approved by Draftsman.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to

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enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 24-42 are directed to creatine amidinohydrolase having  $K_m$  for creatine in the range of 3.5-10.0 mM, a reagent comprising thereof and a method of use thereof.

Claims 24 and 25 add an additional physico-chemical characteristic such as a range of heat stability (claim 24) or a range of pH stability (claim 25). Claims dependent from claim 24 or 25 add at least one of: pH stability, optimum temperature, optimum pH and/or molecular weight. Claim 33 recites  $K_m$  for creatine, optimum temperature, optimum pH and molecular weight.

Thus, the claimed creatine amidinohydrolase having a low  $K_m$  for creatine in the range of 3-10 mM is at most identified by the range of pH and temperature optima, heat and pH stability and molecular weight. Among these properties only molecular weight is given as a point number while the rest is given as a range. Therefore, the claims are drawn to a genus of a creatine amidinohydrolase both naturally occurring and man made having a low  $K_m$  for creatine.

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4D The specification discloses only a three species of the claimed genus, mutants of a creatine amidinohydrolase from *Alcaligenes faecalis* (FERM P-14237, SEQ ID NO:1) having  $K_m$  for creatine of 4.5 mM (FERM BP-5375), 6.5 mM (FERM BP-5374) and 9.0 mM (FERM BP-5376), respectively. These mutants were obtained by random mutation of SEQ ID NO: 2 encoding SEQ ID NO: 1. No sequence of the above mutants are disclosed. <sup>no</sup> Structural features that could distinguish enzymes in the genus from others in the protein class are disclosed. No common structural attributes identify the members of the genus. No structural features imparting said low  $K_m$  are identified.

Moreover, the specification fails to provide any structure: function correlation present in all members of the claimed genus.

Claims 35-37 recite heat stability, pH stability,  $K_m$  for creatine of 4.5+1.0 mM, 6.5+1.0 mM and 9.0+1.0 mM, respectively, optimum temperature, optimum pH and molecular weight. Claim 35 encompasses a genus of creatine amidinohydrolase with  $K_m$  for creatine of 4.5+1.0 mM and range of other properties. The representative number of species is one. The disclosed species is different from the claimed in claim 35 because it has different heat stability and optimum temperature (US 6,080,553, column 11, Table 4). The same concerns with claim 37 (see column 12, Table 6).

Therefore, the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus.

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Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Of note, the specification describes also an isoelectric point that for all three disclosed mutants is 3.5. An isoelectric point is an important characteristic correlating the protein structure and function because only certain mutations are allowed without changing the isoelectric point and retaining other characteristics. An isoelectric point is present in the issued claims but omitted from the currently pending claims.

Claims 24-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a creatine amidinohydrolase having  $K_m$  for creatine of 3-10 mM obtained by mutation of a DNA encoding a wild type creatine amidinohydrolase from *Alcaligenes faecalis* (FERM P-14237, SEQ ID NOs:1-2), does not reasonably provide enablement for a creatine amidinohydrolase with molecular weight of 43 kD having  $K_m$  for creatine of 3-10.0 mM and some other characteristics defined by a range, said enzyme having any structure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, how to make the invention commensurate in scope with these claims.

As discussed above, the claims are directed to creatine amidinohydrolase having a low  $K_m$  for creatine in the range of 3-10 mM of any structure. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard

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to the extremely large number of creatine amidinohydrolase enzymes broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which structure would impart the desired activity requires a detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and amino acid sequence of a single wild type creatine amidinohydrolase from *Alcaligenes faecalis* (FERM P-14237, SEQ ID NO:1) having  $K_m$  for creatine of 15.2 mM. No mutations in its structure resulting in lower  $K_m$  for creatine are disclosed. In general, the state of the art does not allow the predictability of a structure imparting a requisite function.

The specification does not support the broad scope of the claims which encompass any creatine amidinohydrolase of 43 kD having  $K_m$  for creatine of 3-10.0 mM and having any structure and obtained from any source because the specification provides insufficient guidance as to which of the essentially infinite possible structures is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a amidinohydrolase of any structure with the requisite characteristics. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without

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sufficient guidance, determination of a sequence having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite the range of various properties. All of the properties depend on at least pH, temperature and buffer. With regard to the  $K_m$  range, it is defined by the reaction of creatine in a coupling assay. However, said reaction does not necessarily define pH, temperature and buffer under which said  $K_m$  is measured. It is well known in the art that  $K_m$  is highly sensitive to the above parameters.

"pH stability" is unclear because the amount of activity required to be deemed "stable" is not defined.

"Heat stability", the phrase "not more than about 50° C" is confusing. It does not define the amount of activity, and therefore, an enzyme stable at 45° C, for example,



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meets said limitation as well as an enzyme retaining 90% activity at 50° C. Also the range is open ended rendering the metes and bounds of the claims unclear.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 24 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by JP 62-91182.

JP 62-91182 (form PTO-1449) teach a creatine amidinohydrolase having  $K_m$  for creatine of 4.83 mM. It is stable "at near 40° C or below" that is "no more than 50° C" as required by claim 24.

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The enzyme disclosed in JP 62-91182 has molecular weight about 50 kD determined by gel filtration. The enzyme of claim 28 has MW about 43 kD (SDS-PAGE). In both, JP 62-91182 and claim 24, the numbers for MW are given as approximate. Further, the numbers are close enough to attribute the difference between them as resulting from methods. Both methods, gel filtration and SDS-PAGE, do not allow a very precise determination of MW and are expected to give not exactly the same values.

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The reissue oath/declaration filed with this application is defective because it fails to contain a statement that all errors which are being corrected in the reissue application up to the time of filing of the oath/declaration arose without any deceptive intention on the part of the applicant. See 37 CFR 1.175 and MPEP § 1414.

The Declaration mentions one error (isoelectric point) and says that one error arose without deceptive intent. However, an isoelectric point is not the only omitted property. The Declaration does not say that all errors being corrected arose without deceptive intent.

Claims 24-42 are rejected as being based upon a defective reissue Declaration under 35 U.S.C. 251 as set forth above. See 37 CFR 1.175.

The nature of the defect(s) in the Declaration is set forth in the discussion above in this Office action.

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Applicant is reminded of the continuing obligation under 37 CFR 1.56 to timely apprise the Office of any litigation information, or other prior or concurrent proceeding, involving Patent No. 6,080,553, which is material to patentability of the claims under consideration in this reissue application. This obligation rests with each individual associated with the filing and prosecution of this application for reissue. See MPEP §§ 1404, 1442.01 and 1442.04.

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Applicant is notified that any subsequent amendment to the specification and/or claims must comply with 37 CFR 1.121(b).

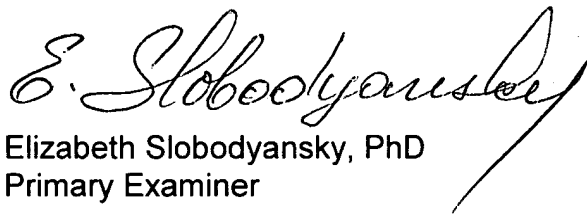
Applicants' offer to surrender patent is noted. The original ribboned copy of the patent has not been surrendered. The original patent, or an affidavit or declaration as to loss or inaccessibility of the original patent, must be received before this reissue application can be allowed. See 37 CFR 1.178.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

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Elizabeth Slobodyansky, PhD  
Primary Examiner

February 5, 2002